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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,184	09/17/2003	Shmuel A. Ben-Sasson	24348-501CIP	5564

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EXAMINER	
MONDESI, ROBERT B	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,184	BEN-SASSON ET AL.	
	Examiner	Art Unit	
	Robert B. Mondesi	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15,25,28-30,39-47,51-69,77-79,82,83,90,97 and 101* is/are pending in the application.

4a) Of the above claim(s) *52-69, 82-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 15, 25, 28-30, 39-47, 51, 77-79, 90, 97, 99 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2003 and 28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to restriction requirement

Applicants' election of Invention Group I, **Claims 1-11, 15, 25, 28-30, 39-47, 50-59, 64-69, 77-79, 82-83, 90, 97, 99 and 101** and the further election of SEQ ID No: 24 (**Claims 97, 99 and 101**), without traverse, in response to the restriction requirement mailed November 26, 2004 is acknowledged.

Applicants' further election of a benzalkonium derivative, without traverse (**Claims 25, and 28-30**), an amphipathic molecule (**Claims 46-47**) in response to the restriction requirement mailed August 18, 2005 is acknowledged.

Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement in regards to above, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore the requirement is still deemed proper and is made FINAL.

Applicants' further election with traverse of insulin (**Claims 10-11 and 15**), aprotinin (**Claims 50-51, 82**) and a non-ionic detergent (**Claims 77-79 and 82-83**) in amendment, filed August 18, 2005 is acknowledged. The traversal is on the ground(s) that the recited agents in claim are members of the same genus and are useful for treating metabolic diseases. This is not found persuasive because the recited agents in claim 15 have completely different structure and function, for example, insulin, calcitonin and the growth hormone have different amino acid sequences and have no regions of shared homology; furthermore the mentioned agents function through entirely different pathways.

The examiner has treated the election of aprotinin (**Claims 50-51, 82**) and a non-ionic detergent (**Claims 77-79 and 82-83**) as species elections.

Therefore the requirement is still deemed proper and is made FINAL.

Claims 52-69, 82 and 83 have been withdrawn for pertaining to non-elected subject matter. **Claims 1-11,15, 25, 28-30, 39-47, 51, 77-79, 90, 97, 99 and 101** are pending and presently under examination.

Priority

The current application filed on September 17, 2003 is a CIP of International application PCT/IB03/00968 filed on February 07, 2003, which in turn claims priority to provisional application 60/355,396 filed February 07, 2002.

Drawings

Applicants' replacement of Figure 2 with replacement sheet in amendment filed February 28, 2005 has been acknowledged and entered.

Specification

The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below: Nucleic acid sequences containing 10 or more nucleotides and amino acid sequences containing 4 or more residues need to be designated with a sequence identifier. Applicants must correct the sequence submissions in the specification on: Presently the amino acid sequence on page 12, line

14 and page 32, line 24 contains four amino acid residues. Appropriate correction is required.

Preliminary Amendment

The preliminary amendment filed March 30, 2004 has been entered.

Information Disclosure Statement

The IDS(s) filed March 10, 2004 and September 10, 2004 have been received and have been signed and considered, a copy of the PTO 1449 is attached to the following document.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 97 is rejected under 35 U.S.C. 102(e) as being anticipated by Henry et al. United States Patent Application Pub No: US2003/0060438.

Henry et al. teach a pharmaceutical composition comprising a peptide comprising the amino acid sequence of SEQ ID NO: 24 (Page 30, amino acid residues 68-90 of SEQ ID NO: 1).

Thus Henry et al. teach all the elements of **claim 97** and this claim is anticipated under 35 USC 102(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 90 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and

(8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

In regards to the composition of the invention and the breadth of the claims the broadest interpretation that applies is a kit comprising a prophylactically or

therapeutically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

2. The nature of the invention.

Then nature of the invention is a kit comprising a prophylactically or therapeutically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

3. The state of prior art.

The state of the art does not teach a kit comprising a prophylactically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

The level of predictability in the art is extremely low since there are no animal studies or human models that have been disclosed by the prior art, involving a kit comprising a prophylactically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

6. The amount of guidance present.

The amount of guidance by the applicants is extremely low since the applicants have not disclosed any animal studies or human models that discuss a kit comprising a

prophylactically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

7. The existence of working examples.

Applicants have not disclosed any examples involving a kit comprising a prophylactically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.

8. The quantity of experimentation necessary.

In the case of a kit comprising a prophylactically effective amount of a composition comprising insulin, benzalkonium and a peptide comprising SEQ ID NO: 24.more experimentation would be required to practice the invention since the specification has not shown to a person skill in the art how to use the invention.

Due to the large quantity of experimentation necessary to provide evidence that the claimed kit comprises a prophylactically effective amount of a composition, the lack of guidance presented in the specification regarding the same, the absence of a working example directed to same, the unpredictable nature of the invention with regards to prophylactically effective amount, the state of the prior art not providing any evidence for any prophylactically effective amount of the said composition, and the breadth of the claims which fails to provide particular steps involved in the preparation of kit comprising a prophylactically effective amount of a composition, the specification fails to teach the skilled artisan in the art how to make and use the invention.

Claim 90 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In **claim 90** the applicants have cited a kit comprising a prophylactically or therapeutically effective amount of the composition as mentioned in claim 2; however the applicants have not indicated in claim 2 or claim 90 as to what the intended prophylactically or therapeutically effective amount is supposed to accomplish.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11,15, 25, 28-30, 39-47, 51, 77 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyurik United Sates Patent Application Pub. No: US 2004/0176476 in view of Henry et al. United States Patent Application Pub No: US2003/0060438.

Gyurik teaches that the composition of the disclosed invention comprises a pharmaceutically-active compound, or a mixture of two or more compounds capable of being delivered across a body membrane (Page 2, section 0014, lines 1-4) and examples of pharmaceutically-active compounds which may be employed in the practice of the present invention include insulin (Page 2, section 0015 lines 1-5).

Gyurik teaches further that the composition of the present invention comprises also an enhancer capable of increasing the rate of passage of the pharmaceutically-active compound through a membrane. Essentially any suitable solid or liquid enhancer or a mixture of such enhancers may be used in the practice of the present invention. Preferred enhancers are characterized by at least one of the following properties: membrane-compatibility; lipophilic nature; low level of irritability or no irritability to the target membrane; emolliency; and being a solid at room temperature when in neat form (Page 3, section 0025, lines 1-10). Membrane-compatible permeation enhancers are particularly preferred for use in the present invention. The term "membrane-compatible permeation enhancer" means a compound which increases the rate of delivery of the pharmaceutically-active compound through the membrane without damage. Examples of lipophilic membrane-compatible enhancers for use in the present invention

include: fatty acids; fatty alcohols; alkyl esters, such as isopropyl myristate and myristyl myristate; and cycloaliphatic enhancers (Page 3, section 0026, lines 1-10).

Gyurik discloses that the pharmaceutical composition of the invention comprises an enzyme inhibitor which is capable of inhibiting breakdown and a suitable inhibitor may be selected form a group consisting leupetin, bestain and aprotinin (Page 6, section 0050, lines 1-19).

Gyurik also teaches that the composition of the present invention may exist in various forms, for example, an oil-in-water emulsion, a water-in-oil emulsion, and a water-in-oil-in-water emulsion. The active compounds of the compositions of the present invention may exist in either the continuous or the dispersed phase or in both phases depending upon whether the compounds are hydrophilic, lipophilic, or amphiphilic. In an example of a preferred embodiment of the present invention, the emulsion comprises oil droplets dispersed in a continuous aqueous phase with a lipophilic enhancer being contained in the oil droplets and a water-soluble pharmaceutically-active compound dissolved in the continuous aqueous phase (Page 4, section 0038, lines 1-13).

Gyurik also discloses that the pharmaceutical composition of the invention comprises insulin and benzalkonium (Page 7 Example 1, Part D and E).

Guyrik teaches that the pharmaceutical composition of the invention be an emulsion in the form of a cream or an ointment (Page 6, section 0052, lines 11-16).

Gyurik does that teach that the pharmaceutical composition of the invention comprises a peptide comprising the amino acid sequence of SEQ ID NO: 24, bile salts or that the composition is in the form of a capsule or tablet.

Henry et al. teach a pharmaceutical composition comprising a peptide comprising the amino acid sequence of SEQ ID NO: 24 (Page 30, amino acid residues 68-90 of SEQ ID NO: 1) and bile salts (Page 16, section –127 lines 1-7).

Henry et al. also teach that pharmaceutical composition of the invention suitable for oral administration may be presented in the form of capsules or tablets (Page 16, section 0123, lines 1-5).

Henry et al. also teach that pharmaceutical compositions comprising the peptides of the invention may also include penetration enhancers in order to enhance the alimentary delivery of composition (Page 16, section 0127, lines 1-7)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine proteins such as insulin and peptides such as SEQ ID NO: 24 with various compounds such as benzalkonium and other penetrating substances for the advantages of a composition that easily penetrates a membrane and causes less irritation, as taught by Gyurik and Henry et al., see Gyurik at page 1, section 004, lines 1-12.

Claims 77-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyurik United Sates Patent Application Pub. No: US 2004/0176476 in view of Henry et al. United States Patent Application Pub No: US2003/0060438 as applied to **claims 1-2** above, and further in view of Ho et al., 2000.

Gyurik and Henry et al. disclose a composition as mentioned above.

Gyurik and Henry et al. do not disclose a composition comprising pluronic F-68.

Ho et al. teach that a multilayer design of pellets for nifedipine was developed using pluronic F-68 to enhance the dissolution rate (Abstract, page 433, line 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine proteins such as insulin and peptides such as SEQ ID NO: 24 with various compounds such as benzalkonium and other penetrating substances for the advantages of a composition that easily penetrates a membrane, causes less irritation that has a release profile comparable with clinical needs, as taught by Gyurik, Henry et al. and Ho et al., see Ho et al., 2000 conclusion, page 440, line 6-7.

Claims 99 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gyurik United Sates Patent Application Pub. No: US 2004/0176476 in view of Henry et al. United States Patent Application Pub No: US2003/0060438 as applied to **claims 1** above, further in view of Davis et al. United States Patent No: 4,179,337.

Gyurik and Henry et al. disclose a composition as mentioned above.

Gyurik and Henry et al. do not disclose a composition wherein the peptide in the composition comprises a chemical modification wherein the chemical modification comprises the attachment of one or more polyethylene glycol residues to the penetrating peptide.

Davis et al disclose a peptide that has been chemically modified in order to have polyethylene glycol residues attached to various amino acids of the peptide (column 2, lines 41-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine proteins such as insulin and peptides such as SEQ ID NO: 24 with various compounds such as benzalkonium and other penetrating substances, wherein the said peptide is pegylated for the advantages of a composition that easily penetrates a membrane, causes less irritation, is non imunogenic and has an increased bioavailability, as taught by Gyurik, Henry et al. and Davis et al., see Gyurik at page 1 section 004, lines 1-12 and Davis et al. at column 2, lines 20-23 and lines 35-40.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert B Mondesi
Patent Examiner
Group 1653
11-07-08

ROBERT A. WAX
PRIMARY EXAMINER